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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,459	11/07/2001	David L. Lewis	Mirus.030.03	3774

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,459	LEWIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *January 18, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Election filed on April 1, 2005. Applicant's election of Group II, claims 11-16 is acknowledged. It is noted that Applicants Election is moot in view of Applicants amendment filed April 1, 2005 to cancel claims 1-10.

Claims 1-10 have been canceled. Claims 11, 12, 15, and 16 have been amended. New claims 17 and 18 are acknowledged.

Claims 11-18 are pending in the instant application.

Claims 11-18 have been examined on the merits.

Information Disclosure Statement

The Information Disclosure Statement filed January 18, 2003 is acknowledged. The references referred to therein have been considered on the merits.

Priority

The reference to priority in the first line of the specification should be updated with current serial numbers where patents have issued. Appropriate correction is required.

Applicants claim the instant application is a continuation in part of 09/450,315, filed 11/29/1999 and claims priority to provisional applications 60/315,394, filed 08/27/2001 and 60/324,155, filed 09/20/2001. The instant application has not been afforded priority to 09/450,315, filed 11/29/1999 since no support could be found for the term "siRNA" in this parent application. Instead, the instant application has been afforded priority to 8/27/2001, which is the earliest date that supports the term "siRNA".

In summary, since the term "siRNA" is not supported in USSN 09/450,315, filed 11/29/1999, the instant application has not been given priority to this filing date. Instead, the instant application has been given priority to provisional application 60/315,394, filed 08/27/2001 since support for the term "siRNA" is found in this application.

Claim Objections

Claims 17 and 18 are objected to because of the following informalities: Claim 17 does not contain a period at the end of the claim. Appropriate correction is required.

Claim 18 contains a typographical error as the word "claim" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitation "wherein the solution is inserted within 2 minutes" in line 1. There is insufficient antecedent basis for this limitation in the claim because none of the claims make reference to the term "solution". Replacement with the term "complex" would overcome the instant rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-17 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-14 and 16-19 of copending Application No. 10/012,804. This is a provisional double patenting rejection since the conflicting claims have not yet

been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the application are drawn to patently indistinguishable subject matter. For example, claim 11 of the instant application is drawn to a process for delivering an siRNA into a cell of a mammal to comprising (a) mixing the siRNA and a compound to form a complex, wherein the zeta potential of the complex is less negative than the zeta potential of the siRNA alone, (b) inserting the complex into a mammalian vessel *in vivo* and, (c) delivering the siRNA to the cell. Claims 12-18 depend from claim 11 and include all the limitations of claim 11 with the further limitations, wherein inserting the complex into a vessel consists of increasing permeability of the vessel; wherein increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the cell is a liver cell; wherein the complex has a positive or negative charge; wherein increasing the pressure consists of increasing volume of fluid within the vessel; and wherein the complex is inserted within 2 minutes. It is noted that the instant specification at page 2, last paragraph contemplates, delivering the complex to a mammalian cell to inhibit nucleic acid expression.

Claim 1 of the copending Application No. 10/012,804 is drawn to a process for delivering an siRNA into a cell of a mammal to inhibit nucleic acid expression comprising (a) making siRNA, (b) inserting the siRNA into a vessel in a mammal, and (c) delivering the siRNA to a parycheymal cell, wherein nucleic acid expression is inhibited. Claims 2-14 and 16-19 depend from claim 1 and include all the limitations of claim 1 with the further limitations, wherein vessel permeability is increased; wherein

increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the vessel is a tail vein or bile duct, wherein the cell is a liver cell; and wherein the siRNA is injected.

Claims 11-17 of the instant application are drawn to a broad genus of mammalian cells, while claims 1-14 and 16-19 of copending Application 10/012,804 are drawn to a species of mammalian cells, namely parenchymal cells. Also, claims 11-17 of the instant application are drawn to a broad genus of siRNA, while claim 19 of copending Application 10/012,804 is drawn to a species of siRNA, namely a siRNA directed against a viral nucleic acid sequence. Additionally, claims 11-17 of the instant application are drawn to a broad genus of vessel, whereas claims 6 and 7 of copending Application 10/012,804 are drawn to a species of vessel, namely a tail vein and bile duct. Thus, species of claims 1-14 and 16-19 of copending Application 10/012,804 anticipate the genus of claims 11-17 of the instant application.

Claims 11-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3-8 and 11-14 of U.S. Patent No. 6,379,966 ('966). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to patently indistinguishable subject matter. For example, claims 11-17 of the instant application are described above in the double patenting over claims 1-14 and 16-19 of copending Application No. 10/012,804.

Claim 1 of ('966) is drawn to a process for delivering a polynucleotide complexed with a compound into an extravascular parenchymal cell comprising (a) mixing the

plynucleotide with a polymer to form a complex, wherein the complex has a zeta potential which is not positive, (b) inserting the polynucleotide into a mammalian blood vessel, (c) increasing permeability of the blood vessel, (d) passing the complex through the blood vessel, (e) delivering the complex into the mammalian extravascular parenchymal cell, and (f) expressing the polynucleotide. Claims 2 and 4-8 depend from claim 1 and include all the limitations of claim 1 with the further limitations, wherein the cell is a liver cell; wherein the polymer has a positive charge; wherein the zeta potential of the complex is negative; wherein increasing the permeability of the blood vessel consists of increasing pressure against blood vessel walls; wherein increasing the pressure consist of increasing a volume of fluid within the blood vessel; and wherein increasing the volume consists of inserting the polynucleotide in a solution into the blood vessel. Claim 11 of ('966) is drawn to a process for delivering a polynucleotide-compound complex into an extracellular parenchymal cells of a mammal comprising (a) making a polynucleotide compound complex, and (b) inserting the complex into a mammalian blood vessel, thereby delivering the polynucleotide to the extravascular parenchymal cell wherein it is expressed. Claims 12-14 of depend from claim 11 and include all the limitations of claim 11 with the further limitations, wherein the parenchymal cell is a liver cell; wherein the permeability of the blood vessel is increased; and wherein increasing the permeability of the blood vessel consists of increasing pressure against blood vessel walls.

Claims 11-17 of the instant application are drawn to a broad genus of mammalian cells, while claims 1, 2, 3-8 and 11-14 of Patent ('966) are drawn to a

species of mammalian cells, namely parenchymal cells. Also, claims 11-17 of the instant application are drawn to a broad genus of vessel, whereas 1, 2, 3-8 and 11-14 of Patent ('966) are drawn to a species of vessel, namely a blood vessel. Thus, species of claims 1, 2, 3-8 and 11-14 of Patent ('966) anticipate the genus of claims 11-17 of the instant application. Claims 1, 2, 3-8 and 11-14 of Patent ('966) are drawn to a broad genus of polynucleotides, while claims 11-17 of the instant application are drawn to a species of polynucleotides, namely siRNA. Thus, species of claims 11-17 of the instant application anticipate the genus of claims 1, 2, 3-8 and 11-14 of Patent ('966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295) in view of Elbashir et al. (Nature, 2001 Vol. 411:494-498) and Zhang et al. (Human Gene Therapy, 1999 Vol. 10:1735-1737).

Claim 11 is drawn to a process for delivering an siRNA into a cell of a mammal to comprising (a) mixing the siRNA and a compound to form a complex, wherein the zeta potential of the complex is less negative than the zeta potential of the siRNA alone, (b) inserting the complex into a mammalian vessel *in vivo* and, (c) delivering the siRNA to the cell. Claims 12-18 depend from claim 11 and include all the limitations of claim 11 with the further limitations, wherein inserting the complex into a vessel consists of increasing permeability of the vessel; wherein increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the cell is a liver cell; wherein the complex has a positive or negative charge; wherein increasing the pressure consists of increasing volume of fluid within the vessel; and wherein the solution is inserted within 2 minutes. It is noted that the instant specification at page 2, last paragraph contemplates, delivering the complex to a mammalian cell to inhibit nucleic acid expression.

Zimmer teach delivering an antisense oligonucleotide complexed with positive and negative charged polymers into a liver cell (see Abstract). Specifically, Zimmer teach mixing an antisense and a polymer, wherein the zeta potential of the complex is less negative than the zeta potential of the antisense alone (see Table 2 and page 290, first full paragraph, which states, "at a lower ratio the surface charge of the nanoparticles is decreased by the ODNs as indicated by a decreased ζ potential").

Zimmer also teach inserting the complex into a mammalian (e.g. tail vein) (see page 292, first full paragraph). Zimmer teach Protocol A, which provides cationically (positively) charged oligonucleotide-loaded nanoparticles and Protocol B, which provides anionically (negatively) oligonucleotide-loaded nanoparticles (see page 287, first and second paragraphs).

Zimmer do not teach a siRNA or inserting a siRNA into a cell of a mammal within 2 minutes.

Elbashir et al. teach siRNA as nucleic acid inhibitors of gene expression in mammalian cells (see Abstract and Figure 3).

Zhang et al. teach that the tail vein injection of naked plasmid DNA enables foreign gene expression in the liver (see Abstract). Zhang et al. also teach maximal gene expression was achieved when the DNA solution was injected within 7-120 seconds (see Figure 1, injection speed).

The term "vessel" is interpreted broadly such that administering the oligonucleotide-loaded nanoparticles via tail vein is equivalent to inserting the polynucleotide into a vessel as claimed. Injection into the tail vein with the oligonucleotide-loaded nanoparticles is equivalent to increasing vessel permeability, by increasing pressure against vessel walls, and increasing a volume of fluid within the vessel as claimed because the method of intravascular injection would inherently increase pressure in the area of injection and at the time of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the tail vein.

It would have been prima facie obvious to one of ordinary skill in the art at the time of filing to devise a process for delivering a nucleic acid into a cell of a mammal for the purpose of nucleic acid therapy as taught by Zimmer. One of ordinary skill in the art would have been motivated to substitute the antisense nucleic acid as taught by Zimmer with the siRNA as instantly claimed since Elbashir et al. teach an siRNA would have been considered to be structurally equivalent to an antisense since both are sequence specific nucleic acid inhibitors of gene expression. Further, see MPEP 2144.06. It would have been obvious to one of ordinary skill in the art to insert the complex within 2 minutes since Zhang et al. taught maximal nucleic acid expression by tail vein injection is achieved when DNA solutions are injected within 7-120 seconds.

One would have had a reasonable expectation of success at delivering an siRNA to a mammalian cell because Zimmer clearly teach the successful delivery of an antisense nucleic acid to a liver cell and since antisense and siRNA are both sequence specific nucleic acid inhibitors of gene expression and since antisense and siRNA are art-recognized functional and structural equivalents, the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time of filing.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
August 10, 2005

ANDREW WANG
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